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Review

PERINATAL ASPECTS OF SARS-CoV-2 INFECTION DURING PREGNANCY: A POTENTIAL CAUSE FOR CONCERN

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SUMMARY – Ever since the beginning of COVID-19 pandemic, uncertainty regarding clinical presentation and differences among various subpopulations exist. With more than 209,870,000 confirmed cases and more than 4,400,000 deaths worldwide, we are facing the new era of health crisis which will undoubtedly impair global health, economic and social circumstances. In the past year, numerous genetic mutations which code SARS-CoV-2 proteins led to the occurrence of new viral strains, with higher transmission rates. Apart from the implementation of vaccination, the effect of SARS-CoV-2 on pregnancy outcome and maternal fetal transmission remains an important concern. Although neonates diagnosed with COVID-19 were mostly asymptomatic or presented with mild disease, the effect on early pregnancy is yet to be evident. While positive finding of SARS-CoV-2 RNA in some samples such as amniotic fluid, placental tissue, cord blood and breast milk exists, additional research should confirm its association with transplacental transmission.

Key words: *SARS-CoV-2; COVID-19; Pregnancy; Vertical transmission; Neonates*

Introduction

Since the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among humans in December 2019, evidence supporting the thesis of maternal-fetal virus transmission and its effects on perinatal outcomes is limited and probably rare. In the 2002-2003 period and in 2015, outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) emerged. Rapidly-spreading infection caused severe respiratory disease with high mortality rates among human population. With more than 209,870,000 confirmed cases and more than 4,400,000 deaths worldwide, we are facing the new era of health crisis which will undoubtedly impair global health, economic and social circumstances[1]. In the past year, numerous genetic mutations which code SARS-CoV-2 proteins led to the occurrence of new viral strains with higher transmission rates. The SARS-CoV-2 Interagency Group and Centers for Disease Control and prevention categorize variants of SARS-CoV-2: Alpha (B.1.1.7), Beta (B.1.351, B.1.351.2, B.1.351.3), Delta (B.1.617.2, AY.1, AY.2, AY.3), and Gamma (P.1, P.1.1, P.1.2) as Variants of Concern. These variants are commonly known as British, South African, Indian and

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Brazilian variants, respectively. Some of the characteristics of these new variants are a higher transmissibility rate, more severe disease, lower rates of neutralization by antibodies caused by prior infection or vaccination, lower detection rates and treatment efficacy[2].

It is believed that pregnant women were particularly susceptible to SARS-CoV infection[3]. Studies on pregnancies and concomitant SARS-CoV or MERS-CoV infections described pregnancy loss, intrauterine fetal growth restriction, or preterm birth[4,5]. In these two former outbreaks, vertical transmission was not confirmed. In 2020, a novel beta-coronavirus, SARS-CoV-2, occurred among humans. Considering some genomic and structural similarities with SARS-CoV, it is to be assumed that SARS-COV-2 could reflect adverse effects on the fetus in early, as well as in late weeks of pregnancy[6]. Thus far, a small number of neonates were diagnosed with COVID-19, among whom disease was mostly asymptomatic or presented with mild symptoms. It is not clear whether infection in these cases was related to vertical transmission[7]. Uncertainty regarding clinical presentation, as well as prediction of differences among various subpopulations has prompted the release of this review, with the aim of summarizing the existing data on epidemiological and clinical characteristics of COVID-19 in pregnancy, possible vertical transmission, as well as maternal and perinatal outcome.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Opposed to all the characteristics and structure of living cells, SARS-CoV-2 is an enveloped virus, containing non-segmented, single-stranded RNA[5]. Crown-like spikes on the outer surface enable viral binding to the host cell receptor and cell membrane fusion[8]. For all other functions, virus utilizes the capacity of the living host. Combining these biological benefits, virus reduces unnecessary energy spending in the environment and directs it towards replication. The host completes the task of information encoded by the virus genome, unaware of its role in the virus lytic cycle. The primary targets of the virus are respiratory epithelial cells. Each infected cell directs all of its resources towards viral RNA replication, eventually resulting in thousands of viral copies. Research has shown that the structure of the receptor-binding gene region required for successful binding of virus to angiotensin-converting enzyme 2 (ACE2) and subsequent cell entry has some resemblances between SARS and SARS-CoV-2[6]. ACE2 has been found to have a pivotal role in entering the cell, since the mechanism of SARS-CoV-2 entering the cell failed using receptors such as aminopeptidase N and dipeptidyl peptidase 4 in experimental studies[6].

Another focus of the researchers' interest is neuropilin-1 receptor protein (NRP1). In addition to finding that NRP1 facilitates the interaction between spike protein and ACE2, detection of this receptor on the outer surface of human cells which lacked ACE2 supports the thesis of NRP1 as an individual factor that allows viral entry[9]. Bats are considered to be animal reservoirs of the virus. Once human subjects are infected, further transmission of the virus is accomplished *via* direct contact with another person. Respiratory droplets or transfer from contaminated surfaces to mucous membranes are the routes of transmission. Some studies indicate aerosol as a possible transmission route, whereas virus was detected in the blood, stool, ocular secretions, and semen. The term basic reproduction number (R0) is an epidemiologic parameter used to calculate the expected number of infected individuals from a single case in a susceptible host population. Series of studies analyzing the basic reproduction number R0 for SARS-CoV-2 in Wuhan, China, reported R0 to be 1.4-3.9, 2.24-3.58, 2.47-2.86[10-12]. For comparison, R0 for SARS-CoV-2 in Italy, which was the European center of COVID-19 outbreak, ranged between 2.43 and 3.10[13].

Classification System for COVID-19 in General Population, Pregnant Women, Fetuses and Neonates

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new beta coronavirus that causes coronavirus disease 2019 (COVID-19). On March 17, 2020, the L. Spallanzani National Institute for Infectious Diseases in Rome, Italy, published recommendations for clinical management of COVID-19 based on case severity for general population. The classification delineates four groups of disease by incorporating the following Modified Early Warning Score (MEWS) clinical deterioration score: asymptomatic or mild infection; stable patient presenting with respiratory and/or systemic symptoms (e.g., MEWS clinical deterioration score <3); clinically unstable patient affected by respiratory symptoms but not in critical condition

(e.g., MEWS clinical deterioration score 3-4); and critical patient (e.g., MEWS clinical deterioration score >4)[14].

In April 2020, an article appeared that elaborated classification system for COVID-19 in pregnant women, fetuses and neonates. Categories of likelihood of infection were developed based on several variables including clinical presentation, results of polymerase chain reaction (PCR) testing, serology, and the possibility of other sources of infection[15]. According to the authors, maternal infection during pregnancy is classified into groups of symptomatic women and those who are asymptomatic but have positive contact history. The group of symptomatic women is subdivided into categories of confirmed, possible, unlikely, and not infected patients, whereas the other group is subclassified into confirmed, unlikely, and not infected patients. These categories are based on the abovementioned variables for likelihood of infection. The authors discourage the use of terms vertical and horizontal transmission and prefer using terminology of congenital infection in intrauterine death/stillbirth (confirmed, possible, unlikely, not infected), congenital infection in live born with or without clinical features in newborn and mother with SARS-CoV-2 infection (confirmed, probable, possible, unlikely, not infected), neonatal infection acquired intrapartum with clinical features in newborn and mother with SARS-CoV-2 (confirmed, probable, possible, unlikely, not infected) or without clinical features (confirmed, possible, not infected), or neonatal infection acquired postnatally (confirmed, probable, not infected), rather than 'vertical' or 'horizontal transmission'[15], in order to specify the exact time of infection.

Characteristics of Respiratory and Immune System in Pregnancy

The widely accepted explanation of pregnancy as a state of maternal immune suppression has been recently renewed and it is believed that the immune system alters during gestation. As pregnancy progresses, immune adaptations of maternal status are observed. Early stages of pregnancy are considered to be proinflammatory to enhance the healing of uterine epithelium after the implantation process. In the mid-part of pregnancy, the immune environment tends to be anti-inflammatory and constitutes protective mechanism to allow fetal development. Approaching the labor, the immune systems tends to be proinflammatory again, and acts by increasing the Th1 proinflammatory cytokines[16]. These conditions, as well as hypervolemia and hypoalbuminemia, may contribute to the complex pathogenesis of acute respiratory distress syndrome (ARDS)[17]. Diffuse alveolar damage leads to progressive respiratory failure[6].

Tumor necrosis factor-alpha (TNF-α) has an important role in the pathophysiology of hypercytokinemia found in secondary hemophagocytic lymphohistiocytosis, triggered by viral infection. The immunomodulatory effect of pregnancy with inhibition of TNF-α by human chorionic gonadotropin and progesterone may have beneficial effect on the low mortality and predominant mild form of COVID-19 among infected pregnant women[18]. However, additional explanation for lesser disease severity and low mortality rate could be younger age of this population group and lower incidence of comorbid disorders.

In treatment approach to pregnant women with COVID-19, physiological adaptations of respiratory system during pregnancy need to be considered, to avoid rapid cardiopulmonary decompensation. In healthy pregnant women, minute ventilation increases in order to compensate increased oxygen consumption and basal metabolic demands. This is accomplished by an increase in tidal volume and decreased functional residual capacity. Eventually, acidosis during pregnancy is more difficult to compensate. Development of pulmonary edema as a complication of preeclampsia, eclampsia, cardiomyopathy, or use of beta-adrenergic tocolytic agents, magnesium sulfate, corticosteroids may further complicate the course of disease[19].

Clinical presentation

The mean incubation period is 5 days, ranging from 2 to 14 days[5]. In general, initial clinical presentation begins with fever, cough, nasal congestion, dyspnea, or pneumonia. Less frequently, patients may present with headache, sputum production, diarrhea, vomiting, malaise and myalgia, decreased smell, taste loss, chest pain[8,20,21]. Pneumonia is a feature of moderate and severe forms of disease and typically occurs within 14 days after the onset of symptoms[22]. Severe forms of pneumonia may progress to ARDS as it is the case in 17%-29% of hospitalized patients[5], whereas reliable data on pregnant women are lacking. Similar to children, a proportion of adults may develop rare com-

plication after COVID-19 infection, termed as multisystem inflammatory syndrome in adults (MIS-A). The diagnosis of MIS-A is made on clinical criteria and laboratory evidence including occurrence of severe cardiac illness or rash accompanied with non-purulent conjunctivitis, neurological impairment, shock, hypotension, gastrointestinal symptoms and thrombocytopenia, and laboratory confirmation of inflammation and recent SARS-CoV-2 infection[23].

The majority of pregnant patients with COVID-19 present with fever, cough, leukopenia and raised C-reactive protein (CRP). Studies which compared the clinical manifestation of COVID-19 among pregnant and non-pregnant women showed the incidence of fever, chills, myalgia and headache to be lower among pregnant women. Even though fever is considered a common symptom, many patients are afebrile, with the presence of fever being documented after delivery[24].

In a systematic review that evaluated 114 pregnant women, the most frequently reported symptoms were fever and cough, followed by tiredness, diarrhea, dyspnea, sore throat, and muscle pain. Based on the Chinese Novel Coronavirus Pneumonia Diagnosis and Treatment Protocols, 110 patients exhibited mild or regular forms of COVID-19, whereas severe form of disease was present in 6 patients[25]. In a series of 43 pregnant women with COVID-19 during the spreading of virus in New York, the most frequently reported symptoms were dry cough, fever and myalgia[3]. According to recent studies, time between delivery and onset of symptoms ranged between 1 and 7 days, whereas some women presented with symptoms after delivery[24].

In November, 2020, US Department of Health and Human Services, Centers for Disease Control and Prevention released a report on the characteristics of symptomatic women of reproductive age with laboratory-confirmed infection with SARS-CoV-2e according to the pregnancy status. Analysis of data on 409,462 symptomatic women (23,434 pregnant and 386,028 nonpregnant women) showed that pregnant women had a higher rate of admission to an intensive care unit (ICU; 10.5 *vs*. 3.9 *per* 1000 cases), required invasive ventilation (2.9 *vs*. 1.1 *per* 1000 cases) and extracorporeal membrane oxygenation (ECMO) (0.7 *vs.* 0.3 *per* 1000). The mortality rate was higher in the group of pregnant women (1.5 *vs*. 1.2 *per* 1000 cases)[26].

There is ongoing debate on whether pregnancy as a state of hypercoagulation may be further complicated by the development of thrombosis and pulmonary emboli as a consequence of COVID-19, especially in patients with inherent hypercoagulability[21,27-30]. So far, there is no convincing evidence for the increased incidence of thromboembolic incidents and subsequent mortality rate among pregnant patients with COVID-19. Hence, strong evidence to support prophylactic anticoagulation in pregnant patients with COVID-19 is lacking[31,32].

According to data of a large systematic review and meta-analysis which included 77 studies, risk factors linked with severe COVID-19 were advanced maternal age, obesity, chronic hypertension and pre-existing diabetes[33], which also independently influence outcomes of uncomplicated pregnancies[34-37]. Among the studied population, 4% of participants required admission to ICU, 3% required invasive ventilation, and 0.4% were treated by ECMO. The fatality rate was 0.1%[33].

The higher mortality rate of pregnant patients with COVID-19 in some Latin American countries should be critically analyzed as a consequence of health care services, epidemiological measures, and higher incidence of cesarean section rather than the disease itself[38].

Laboratory evaluation in pregnancy complicated with COVID-19

In cases of confirmed COVID-19, laboratory evaluation in the majority of pregnant women reveal lymphopenia, low platelets, and elevated transaminases, elevated CRP and D-dimer[39]. Data extracted from 50 pregnant patients with COVID-19 exhibited mean leukocyte levels of 9.51×10^9 cells/L and CRP of 16.83 mg/L, suggesting no major divergence (normal pregnancy range: white blood cell (WBC) 5.7-13.6, 5.6-14.8, 5.6-16.9 for the first, second and third trimester, respectively, CRP 0.4-20.3, 0.4-8.1 for second and third trimester)[22,26]. However, in a systematic review and meta-analysis which included 24 studies and a total number of 1100 Chinese, European and North American pregnant women with COVID-19, the most common laboratory abnormalities identified were elevated levels of CRP and lymphocytopenia, without specifying mean values[40]. Allotey *et al.* report that the most common laboratory findings in

pregnant or recently pregnant women with suspected or confirmed COVID-19 were raised CRP levels, lymphopenia, raised WBC count (49%, 35% and 27%, respectively), followed by elevated procalcitonin levels, liver function tests and thrombocytopenia (21%, 11% and 8%, respectively)[33]. In an attempt to address laboratory factors associated with disease severity or mortality, a team led by Argentina researchers showed the risk of disease severity to be increased in the presence of elevated cardiac troponin levels, WBC levels and high CRP levels, with high certainty of evidence. A factor associated with mortality, supported by high certainty of evidence, was low platelet count. Evidence for moderate certainty for disease severity exists for high levels of D-dimer, lactate dehydrogenase (LDH), aspartate transaminase (AST), creatinine, neutrophil count, brain natriuretic peptide, blood urea nitrogen, creatine phosphokinase, total bilirubin, interleukin-6 (IL-6), and decrease in lymphocyte count and albumin. Moderate levels of evidence exist for increase in the levels of troponins, WBC, lactate, D-dimer, LDH, CRP, AST, creatinine, decrease in lymphocyte count, albumin and mortality from COVID-19[41].

Pregnancy outcome

Most cases of COVID-19 were reported in the second and third trimester of pregnancy. Retrospective cohort studies comparing the outcome of early pregnancies between asymptomatic COVID-19 patients and healthy controls have shown that the total numbers of any type of miscarriages did not differ between study groups[30].

Seeking to address the impact of maternal infection with SARS-CoV-2 in first trimester on fetal development, Freiesleben *et al*. analyzed the nuchal transparency thickness at first trimester scan in pregnant women with positive results of serology testing for SARS-CoV-2 antibodies. Furthermore, the authors evaluated the risk of early pregnancy loss among women with previous infection with SARS-CoV-2. No significant difference in nuchal translucency thickness was found in fetuses of pregnant women previously infected with SARS-CoV-2. Infection with SARS-CoV-2 was not a risk factor for early pregnancy loss[42]. Infection in third trimester may result in preterm birth, low birth weight, fetal distress, neonatal asphyxia, stillbirth, and neonatal death[25]. Recently, Lima *et al*. report a case of a fetus prenatally diagnosed with significant pericardial effusion. Maternal serologic testing for SARS-CoV-2 was performed and showed positive IgM and IgG. Following emergent cesarean section at 33 weeks of gestation, the newborn was diagnosed with pericarditis caused by maternal-fetal transmission. In the absence of results positive for other common conatal infection, the newborn's nasal and oropharyngeal swabs were positive for SARS-CoV-2. Serologic test performed in the newborn was positive for IgG antibodies[43].

In a population of pregnant patients with COVID-19, the rate of preterm birth varies from 17% to 21.8% of cases[33,44]. Since the rates of spontaneous preterm birth do not differ from general population significantly, these results may reflect a substantial proportion of iatrogenic induction of labor. In a recently published systematic review and meta-analysis which included 17 studies, perinatal deaths occurred in less than 1%[44]. Although Allotey *et al*. report on 18 stillbirths in a total number of 2837 offspring and 6 neonatal deaths in 1728 neonates of mothers positive for SARS-CoV-2, no significant risk compared to mothers without the disease was found[33].

While Khalil *et al*. report on the incidence of cesarean section of 48.3%[44], in the analysis which included 114 pregnant women with COVID-19, Yang *et al*. report on the incidence of cesarean section as high as 91%. This high rate of cesarean section was attributed to preeclampsia, fetal distress, previous cesarean section, and fear of transmission to the child during vaginal delivery[25]. The reported adverse neonatal and fetal outcomes were preterm birth (21.3%), fetal distress (10.7%), low birth weight (<2500 g, 5.3%), stillbirth (1.2%), neonatal death (1.2%) and neonatal asphyxia (1.2%)[25]. Even though there is no recommendation for cesarean section in women with COVID-19, recent studies report that most clinicians favor this approach.

Diagnosis

The standard testing method for SARS-CoV-2 include high-throughput sequencing or nucleic acid amplification tests (real-time reverse transcription-polymerase chain reaction, RT-PCR) for detection of genetic components of viral RNA, obtained from blood, amniotic fluid and other body fluid samples such as bronchoalveolar lavage fluid (BALF), sputum, pharyngeal swabs, urine, or stool. The sensitivity of RT-PCR is reported to be 30%-60%. Out of 4880 human samples being tested for COVID-19, BALF had a 100%

positive rate for SARS-CoV-2, followed by sputum and pharyngeal swabs with positive rates of 49.12% and 38.25%, respectively[44]. The majority of current studies evaluating viral RNA in amniotic fluid, placental tissue, cord blood and breast milk of COVID-19 positive patients proved no positive results[46]. Vivanti *et al*. report a case of confirmed SARS-CoV-2 infection in a neonate presenting with neurological symptoms. The neonate was delivered *via* cesarean section. Amniotic fluid obtained prior to rupture of membranes, as well as placental tissue, blood, BALF, nasopharyngeal and rectal swabs were all positive for E and S genes of SARS-CoV-2[47].

In addition to high-throughput sequencing and RT-PCR, pathologic examination and detection of organ specific damage can further support the diagnosis. Pathologic examination of placenta showed perivillous fibrin deposition, infarction, and acute and chronic intervillousitis[47].

The role of serology in detecting infected newborns whose mothers acquired infection at some time near delivery may not be helpful since the time for developing antibodies may be absent[15]. Due to the time required for the antibodies to develop, the role of this method in early diagnosis of newborn infection is debatable.

The IgM antibodies do not cross the placental barrier. Thus, positive results of IgM antibodies in newborns suggest that patients developed their own antibodies[25,48]. Appearing later, IgG antibodies cross the placental barrier and may indicate both maternal and newborn infection. Existing evidence indicate that type IgM and IgG can be detected in blood two to three weeks after clinical onset of the disease in patients infected with SARS-CoV-2. In case of a newborn delivered *via* cesarean section by a mother diagnosed with COVID-19, antibody testing was performed at two hours of age. Elevated levels of SARS-CoV-2 IgG and IgM were detected. The levels of IL-6, IL-10 and WBC count were increased. Nasopharyngeal swabs tested with RT-PCR were repeatedly negative for SARS-CoV-2. These findings may imply vertical transmission[48].

In the editorial that critically evaluates positive findings of IgM in neonates whose mothers were infected with SARS-CoV-2 during pregnancy, Kimberlin and Stagno emphasize rapid decline of IgM levels in comparison to congenital Zika infection and rubella syndrome, suggesting the possibility of these results as artifacts. In cases of other congenital infections, findings of IgM can be explained with cross-reactivity and different specificity rates among various types of common viruses, as well as the finding of rheumatoid factor or partial removal of IgG as it is the case in congenital rubella syndrome[49]. Furthermore, a finding of antibodies that typically do not cross the placental barrier may suggest a potential placental damage.

Maternal-fetal transmission

Placenta as a prime component of the maternal-fetal interface provides a barrier for various infectious agents. Cells of syncytiotrophoblast, exposed to certain amount of maternal blood containing pathogens, exhibit resistance that increases as placenta differentiates[50]. While susceptibility patterns and rates of transmission for other viruses have been documented, transmission mechanism of SARS-CoV-2 remains unclear. It is believed that transmembrane ACE2 receptor has a role in placental angiogenesis, trophoblast proliferation, and invasion by stimulating vasodilatation by releasing angiotensin 1-7[51]. Analysis of single-cell RNA sequencing (scRNA-seq) data found the presence of ACE2 receptors in stromal, perivascular cells of decidua, as well as cytotrophoblast and syncytiotrophoblast of placenta[52]. The presence of these receptors in placenta, which serves as a barrier for various infectious agents, increases as pregnancy advances with peak expression at term[53]. Furthermore, investigating ACE2 receptors in tissue of fetal organs, their expression was confirmed in the heart cardiomyocytes, smooth muscle cells and pericytes, as well as in liver fibroblast, hepatocytes, airway epithelial cells, and arterial endothelial cells[52].

According to Facchetti *et al.*, the presence of SARS-CoV-2 in placenta was demonstrated by detecting viral nucleic acid in cells of syncytiotrophoblast, using the RNA *in situ* hybridization method. Immunohistochemistry methods identified infiltrates of monocyte macrophages, mature and immature neutrophils, as well as platelet depositions in the intervillous space[54].

Findings of ACE receptors, SARS-CoV-2 antigens and RNA in placental tissue support the possibility of transplacental transmission of SARS-CoV-2.

The term vertical transmission refers to maternal-fetal transmission of infection acquired *in utero* (transplacental or ascending infections) during deliv-

ery or postpartum[54]. Positive finding of SARS-CoV-2 in newborns after delivery can be the result of breastfeeding or spreading of viral particles from persons in close contact. Environmental transmission in these cases should be distinguished from vertical transmission.

Most maternal and neonatal biological samples used to identify vertical transmission are nasopharyngeal swabs, plasma, vaginal secretions and stool specimens, amniotic fluid, breastmilk samples, placental tissue, cord blood, neonatal blood, gastric fluid, oropharyngeal, nasopharyngeal and anal swab.

Some studies have reported on infants with positive results of testing for SARS-CoV-2 which was performed in the first few days of life. However, strong evidence that further support either vertical or horizontal transmission in these cases is lacking. The first of studies analyzing characteristics and outcomes of pregnant women with COVID-19 was the one published by Chen *et al*. In this case series, all biologic specimens obtained from infants and tested for SARS-CoV-2 by use of quantitative RT-PCR (qRT-PCR) were negative[18]. Publications that followed report no or a sporadic number of infected infants born to mothers with COVID-19 during pregnancies[17,56-58].

A recently published meta-analysis of 176 neonates infected with SARS-CoV-2 showed that 70% of infection resulted from environmental spread and 30% were likely to be vertically transmitted. In the study population, information needed for classification of the infection was available for 122 neonates. Based on the aforementioned classification proposed by Shah *et al*.[15], the following results were obtained: probable postpartum acquired 63.9%, confirmed congenital 5.7%, probable congenital 4.9%, possible congenital 1.6%, confirmed intrapartum acquired 3.3%, probable intrapartum acquired 3.3%, possible intrapartum acquired 10.7%, and confirmed postpartum acquired infections 6.6%. The authors report confirmed vertical infections in 9% of cases[59].

Cesarean section is considered to be a reasonable option of delivery in an attempt to minimize the risk of newborn infection, as well as the possible perinatal and maternal complications.

However, this mode of delivery is indicated for limited cases of infection to prevent vertical transmission. Although a significant number of cesarean deliveries are reported in women with COVID-19, current guidelines do not advocate it as a strict indication. According to guidelines, cesarean delivery in women with COVID-19 should be performed for obstetric indications with emphasis on individualized approach.

If expectant mother has complications of COVID-19 in the form of respiratory insufficiency or organ system failure in the context of multiorgan failure, cesarean section is even more justified in order to protect both the mother and the child. Expression of ACE2 protein in gastrointestinal epithelia may produce symptoms of diarrhea, nausea, vomiting, and/or abdominal discomfort even before the onset of respiratory symptoms in some patients infected with SARS-CoV-2[60]. Detection of viral RNA in fecal samples may indicate a potential risk of fecal-oral transmission which can last even after viral clearance from the respiratory tract. For now, vaginal samples need to be investigated. Since vaginal delivery poses a high-risk procedure for stool contamination of the child, this way of delivery may potentially pose a risk in symptomatic patients. Knowing that 16% of pregnant women with COVID-19 are asymptomatic, measures of precaution should be followed[61].

Convincing evidence for SARS-CoV-2 transmission *via* breast milk based on case-control or cohort studies is missing. Although transmission of SARS-CoV-2 through breast milk cannot be excluded, it remains questionable whether sporadic findings of SARS-CoV-2 RNA in breast milk may suggest maternal infant transmission[61,62], since infection in these infants can be explained by small-particle aerosols or droplets during breastfeeding[63]. Hence, current recommendations for managing neonates with suspected or confirmed COVID-19 support continuing breastfeeding, as well as skin to skin contact, rooming in and kangaroo care. Precautionary measures advised include use of mask and hand hygiene before and after feeding[63,64].

Conclusion

In times of rapidly spreading COVID-19 pandemic and subpopulation diversities in clinical presentation, special attention needs to be directed towards the effect of SARS-CoV-2 infection on pregnancy and neonatal outcome. Experience with previous coronavirus infections taught us to anticipate some adverse effects. Even though unfavorable outcomes of preg-

nancies with concomitant COVID-19 have been reported, a small number of neonates were diagnosed with COVID-19, among whom disease was mostly asymptomatic or presented with mild symptoms. In the last few months, extensive research was published about SARS-CoV-2 infection and potential maternal fetal transmission. So far, evidence for vertical transmission is rare. Nevertheless, we eagerly expect further clinical and epidemiological studies which will uncover transmission routes of SARS-CoV-2 virus among pregnant women and their children.

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Sažetak

PERINATALNE ZNAČAJKE INFEKCIJE VIRUSOM SARS-CoV-2 U TRUDNOĆI: MOGUĆ RAZLOG ZA ZABRINUTOST

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Od početka pandemije COVID-19 do danas tijek bolesti među različitim subpopulacijama ljudi nije do kraja poznat. Diljem svijeta potvrđeno je više od 209.870.000 oboljelih, ali i više od 4.400.000 smrtnih slučajeva. Nalazimo se u vremenu globalne krize, suočeni s njezinim posljedicama na zdravlje ljudi, ekonomiju i društvo. Protekle godine su brojne genske mutacije koje dovode do strukturnih promjena proteina SARS-CoV-2 dovele do pojave novih sojeva virusa s većom transmisijom. Bez obzira na uvođenje cijepljenja učinak SARS-CoV-2 na ishod trudnoće i prijenos virusa s majke na dijete i dalje su važan predmet interesa. Zasad je poznato da je novorođenčad s COVID-19 najčešće asimptomatska ili s blagom kliničkom slikom, a utjecaj infekcije na ranu trudnoću bit će tek vidljiv. Iako je RNK SARS-CoV-2 potvrđena u uzorcima plodove vode, posteljičnog tkiva, krvi pupkovine i u majčinu mlijeku potrebna su dodatna istraživanja koja će potvrditi njezinu povezanost s transplacentnim prijenosom.

Ključne riječi: *SARS-CoV-2; COVID-19; Trudnoća; Vertikalni prijenos; Novorođenčad*